

HIV-Associated Lipodystrophy Syndrome

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ABSTRACT

In recent years, lipodystrophy and its related complications have become one of the major problems confronting HIV-infected patients on antiretroviral therapy. More than ten years after having been described for the first time, comprehensive knowledge of its underlying molecular basis, the natural history of body fat changes and metabolic abnormalities, and even a working definition of lipodystrophy are all still lacking. No standardized objective assessment of body fat has been incorporated into clinical practice for patient monitoring. Although a huge amount of data has been generated, no clinically proven treatment for any feature of lipodystrophy is currently available. The only intervention that has been shown to reverse lipodystrophy had been the discontinuation of thymidine analogues, although even then the results obtained are at most partial or modest. Recently published studies using uridine (NucleomaxX) and pravastatin resulted in a significant increase of subcutaneous fat. The potential for reversing lipodystrophy once it has developed is limited, but promising results in preventing it are obtained with thymidine analogue-sparing initial antiretroviral regimens. These results raise the question of whether we may be facing a definitive solution to the lipodystrophy syndrome.

Key words: lipodystrophy, metabolic abnormalities, HIV, HAART

Introduction

Lipodystrophy in HIV-1-infected patients represents an adverse effect of antiretroviral therapy not limited to a specific drug or class of drugs.

HIV-associated lipodystrophy may affect up to half or more of HIV-infected patients receiving antiretroviral therapy^{1,2}. The word »lipodystrophy« has an imprecise meaning, and as understanding of the problem has become more sophisticated, the definition of lipodystrophy has been further obscured. »Lipodystrophy« is generally used to refer to a syndrome of peripheral fat wasting (lipoatrophy) and central fat accumulation (lipohypertrophy). However, at present, it is not completely known whether lipodystrophy is one unique syndrome or several different overlapping syndromes.

Several metabolic abnormalities, such as dyslipidemia and insulin resistance, have also been reported in patients receiving antiretroviral therapy. These metabolic changes may increase the risk for cardiovascular disease³. Other events such as hyperlactatemia, low bone mineral density, avascular necrosis, hypogonadism and hypertension have been described, though their relationship with lipodystrophy syndrome has not been clearly established.

In addition to these medical issues, body fat changes are disfiguring, can be stigmatizing, and may lead to social isolation, and thus a poorer adherence to and eventual failure of antiretroviral therapy. Knowledge of some aspects of this problem has increased in recent years, but many important questions remain unanswered.

Definition of Lipodystrophy

Lipodystrophy emerged as an unexpected problem in the field of HIV disease. To date, the most common way to diagnose lipodystrophy is by subjective description of body fat changes. Two multicenter studies have recently undertaken the task of establishing objective criteria for defining lipodystrophy. The Lipodystrophy Case Definition Study compared patients with and without evident clinical signs of lipodystrophy, agreed upon by the patient and the doctor. Laboratory, anthropometrical, and radiology (including CT scan and dual X-absorptiometry or DEXA) data were compared between the two groups of patients, with a goal of creating a quantitative scoring system by which to define lipodystrophy⁴. The generated definition of lipodystrophy had an 80% sensitivity and

specificity, but was shown to be too complex to be used as a regular part of clinical practice. The Fat Redistribution and Metabolic Changes in HIV Infection (FRAM) study compared laboratory, anthropometric, and radiologic data of HIV-infected and non-HIV-infected subjects. The FRAM study showed that generalized lipoatrophy, not lipohypertrophy, was the only distinctive body fat change associated with HIV infection⁵. The results of the FRAM study do not explain why the prevalence of intra-abdominal obesity is so high in HIV-infected individuals. However, other studies also agree that lipoatrophy is the hallmark of body fat changes in HIV-infected people^{6,7}.

Measurement

Objective criteria for diagnosing lipodystrophy are still not established. The word lipodystrophy has a vague meaning, becoming even much more vague as the problem has become more complex over time. Patient description of fat redistribution, confirmed by physician examination, remains the preferred method for describing the problem individually. But objective criteria for diagnosing lipodystrophy are still not established. The lack of standardized values of fat gain in the general population and the heterogeneity of the clinical manifestation of lipodystrophy complicate matters even further. There is no gold-standard method for measuring body fat. However, several techniques have been used: anthropometry, bioimpedance analysis, DEXA, computed tomography, magnetic resonance imaging and ultrasonography. Each of these techniques has limitations. Anthropometry and bioimpedance analysis cannot measure regional body fat. Computed tomography and magnetic resonance imaging are expensive, and use may be restricted^{8,9}. Ultrasonography is promising because of its simplicity, safety, availability and low cost, although it is more operator-dependent than other techniques. DEXA has gained popularity and is probably most extensively used at present^{10,11}. Few data are available on the comparison of these objective techniques for measuring regional body fat. It seems that the measurement of absolute values of regional fat is highly correlated¹².

Another important issue is whether it is necessary to incorporate objective measurements of regional body fat into clinical practice, for anything other than investigational purposes. Despite enthusiasm for determining the best method for quantifying regional fat, the clinical utility of such measurements has not been established. Availability and cost pose further barriers to clinical use of objective measurement of regional body fat. However, objective evolution of even minimal changes needs to be measured, in order to prevent or diminish further progression as well as to accurately evaluate possible interventions.

Pathological Mechanisms

The etiology of HIV-associated lipodystrophy seems to be multifactorial. Several studies have demonstrated

that various risk factors may play an important role in the pathogenesis of lipodystrophy. Risk factors can be divided into several groups: host factors (gender, age, race, genetic factors, initial total body fat content), environmental factors (nutrition, exercise level) antiretroviral therapy (duration of and drugs used), immunological response, HCV coinfection, as well as HIV-1 infection itself. Underlying environmental and host factors are difficult or impossible to modify, and clinical trials have clearly demonstrated that the contribution of choice and duration of antiviral therapy are key risk factors in the development of body fat changes. The choice of initial antiretroviral therapy is very important in preventing development of lipodystrophy. For example, we now know that thymidine analogue-sparing first line regimens cause less lipoatrophy than thymidine analogue-containing regimens^{13,14}.

Managing HIV Lipodystrophy

So far, there is no adequate treatment to reverse lipodystrophy. Diet is of little use by itself, unless dietary abnormalities are present¹⁵. Exercise may lead to a partial beneficial decrease of central fat accumulation and triglycerides, but at the expense of increased peripheral fat wasting^{16,17}.

The impact of discontinuing antiretroviral drugs supposedly involved in the pathogenesis of lipodystrophy syndrome has been assessed in different studies. The earliest studies discontinued protease inhibitors^{18,19}. In general, switching protease inhibitors may improve metabolic abnormalities, but the impact on body fat is very scarce or null. Switching thymidine analogues (most data coming from stavudine and/or zidovudine discontinuation) has been the only intervention seen to improve lipoatrophy^{20–23}.

The effect of discontinuing all antiretroviral therapy on the evolution of lipid abnormalities and body fat is poorly understood. Some preliminary data obtained from a group of well-controlled patients with primary HIV infection show a gain of total and regional fat during consecutive cycles of structured treatment interruptions^{24,25}. This issue is being addressed in ongoing large-scale studies.

Treatment with thiazolidinediones and leptin has shown good results in a population of non-HIV-infected patients with genetic and autoimmune lipodystrophy^{26,27}. Moreover, two small-uncontrolled studies suggested that rosiglitazone might contribute to fat gain regardless of ongoing antiretroviral therapy^{28,29}. Randomized, placebo-controlled studies, though, have shown that rosiglitazone does not improve fat mass in HIV-lipoatrophy, and can possibly worsen dyslipidaemia despite an improvement of insulin sensitivity^{29,30}.

Data from randomised studies comparing effects of metformin, gemfibrozil and placebo in patients receiving HAART have found less fat loss with gemfibrozil than with placebo, no effect of metformin, while all patients lost fat over time³¹.

One recently published study reported a significant increase of subcutaneous fat with twelve weeks of treatment with pravastatin³². Pravastatin use has not been previously reported to have any effect on subcutaneous fat, but these results suggest there may be a place for pravastatin in the treatment of HIV-related lipodystrophy.

Uridine use may provide an additional treatment option. In a study designed to investigate the effect of uridine (36g NucleomaxX three times a day for 10 days/month over 3 months) an increase in the amount of subcutaneous fat was observed³³.

These findings need to be further investigated in large randomized prospective trials.

Since current treatments for lipodystrophy take time and may provide only modest improvement, there is a growing demand for interventions with immediate results. Advances in the field of plastic and reparatory surgery have proven to be popular treatment options. Liposuction performed in some patients with severe buffalo hump or increased subcutaneous fat deposits showed good short-term results, but some patients re-accumulated fat over the following months^{34,35}. Unfortunately, there is still no treatment available for patients with visceral fat accumulation.

Implant surgery for facial lipodystrophy can be performed using permanent or biodegradable implants such as polylactic or hyaluronic acid, or autologous fat from the dorsocervical or subcutaneous abdominal area^{36,37}. Treatment of facial lipodystrophy by injecting autologous adipose tissue (Coleman's lipostructure) seems to be a satisfactory and cost-effective option to treat facial lipodystrophy if there is an existing source of fat graft³⁸. Prospective studies are ongoing to assess the durability and potential differences among different surgical interventions³⁹.

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Conclusions

HAART has dramatically altered the natural history of HIV disease⁴⁰. HIV-related lipodystrophy has emerged as one of most prevalent and worrisome problems for HIV-infected patients now when significant improvement in long-term prognosis of HIV-related immune suppression is provided. Great improvements in the understanding of lipodystrophy have been achieved, though there is still much to be learned. A definition of lipodystrophy has yet to be established. A clinically proven definitive treatment for any feature of lipodystrophy does not exist.

The only intervention that has been shown to revert lipodystrophy had been the discontinuation of thymidine analogues, although results obtained are at best partial and slow. Structured therapy interruption has become an increasingly popular strategy aimed among other things, preventing antiretroviral drug toxicity, but few objective data exist on the impact on the body composition of HIV-infected patients.

Studies using pravastatin and uridine have led to encouraging reversal of subcutaneous fat loss, and further studies are ongoing. Plastic surgery may give satisfactory, though not always permanent, aesthetic results in the absence of other definitive options.

Acknowledgements

The author kindly thanks Rob Camp, Treatment Action Group in New York and Ilana Richman, University of California San Francisco for making insightful commentaries.

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LIPODISTROFIJA POVEZANA S HIV-INFЕКЦИЈOM

SAŽETAK

Lipodistrofija i komplikacije povezane s njom postale su proteklih godina jedan od glavnih problema koje susreću bolesnici zaraženi HIV-om koji primaju antiretrovirusne lijekove. Deset godina nakon prvih opisa znanje o molekularnoj podlozi, prirodnom tijeku i metaboličkim abnormalnostima pa čak i radna definicija lipodistrofije još nedostaju. Nije uveden niti standardiziran postupak procjene tjelesnog masnog tkiva u kliničku praksu. Uprkos niza istraživanja zasad ne postoji klinički dokazano liječenje bilo kojeg oblika lipodistrofije. Jedina intervencija koja je pokazala regresiju lipoatrofije je prekid liječenja analogima timidina, iako je i u toj situaciji učinak bio djelomičan ili skroman. Nedavno objavljena istraživanja primjene uridina (NucleomaxX) i pravastatina pokazala su značajno povećanje potkožnog masnog tkiva. Mogućnosti popravljivanja lipodistrofije kada je ona već razvijena su ograničene ali ohrabruju rezultati sprječavanja nastanka lipodistrofije kada se u početnom antiretrovirusnom liječenju primjenjuju lijekovi koji nisu analozi timidina. Ovi rezultati postavljaju pitanje da li smo suočeni s konačnim rješenjem sindroma lipodistrofije.